REMARKS

Claim Amendments

Claims 1-46 were present in the application. Claims 1, 11, 28, 30, 32-40 and 46 are amended. Claims 6-8, 12-27, 29 and 41-45 are canceled without prejudice; claims 7, 12-23, 25 and 29 having been previously canceled and claims 6, 8, 24, 26-27 and 41-45 canceled herein. New claims 47 - 59 are added. Claims 1-5, 9-11, 28, 30-40 and 46-59 are presently subject to examination, and includes six independent claims and 34 total claims. New claim fees for three total claims are believed due, and are submitted herewith.

Claim 1 is amended to more particularly describe and distinctly claim the invention. The preamble is amended to provide for determining the presence of an acute renal tubular cell injury (inherent support is found, for example, in the original claim that provides "detection" of a renal tubular cell injury, and express support is found, for example, in para. [0063], the last sentence of para. [0100] and the last sentence of para. [0101] for "acute" renal injuries). The claim is also amended to add a step (d) of correlating the detected antibody-NGAL complex from step (c) to the presence of the acute renal tubular cell injury (express support is found, for example, in paragraphs [0098], [0100] and [0101]).

Claim 11 is amended to correct a minor typographical error.

Claim 28 is amended to more particularly describe and distinctly claim the invention. The preamble is amended to provide for determining the presence of an acute renal tubular cell injury (inherent support is found, for example, in the original claim that provides "detection" of a renal tubular cell injury, and express support is found, for example, in para. [0063], the last sentence of para. [0100] and the last sentence of para. [0101] for "acute" renal injuries). The claim is also amended in step (a) to provide that the injury is an acute renal tubular cell injury caused by an event, and to step (c) to provide "correlating the level of the antibody-NGAL complex with the presence of the acute renal tubular cell injury" (express support is found, for example, in paragraphs [0098], [0100] and [0101]).

Claim 30 is amended to more particularly describe and distinctly claim the invention. The preamble is amended to provide for determining the presence of an acute renal tubular cell injury (inherent support is found, for example, in original claim 1 that provides "detection" of a renal tubular cell injury, and express support is found, for example, in para. [0063], the last sentence of para. [0100] and the last sentence of para. [0101] for "acute" renal injuries). The claim is also amended in step (a) to provide that the mammalian subject is

suspected of having an acute renal tubular cell injury, and in step (b) to provide correlating the presence of NGAL in the urine sample to the presence of the acute renal tubular cell injury (express support is found, for example, in paragraphs [0098], [0128] and [0129]).

Claims 32 is amended to correct antecedent basis to acute renal tubular cell injuries, and to delete the member of the group "another injury that affects the tubular cells of the kidney".

Claim 33 is amended to more particularly describe and distinctly claim the invention, regarding the sampling of the first urine output following the acute renal tubular cell injury, and to provide antecedent basis.

Claim 34 is amended to correct antecedent basis to acute renal tubular cell injury.

Claim 35 is amended to correct claim dependency, to add a sampling time period of 3 hours, and to provide that the period of time is following the acute renal tubular cell injury caused by the event. Support is found, for example, at Fig. 12 and 13 and paras. [0031] and [0032].

Claim 36 is amended to provide that the acute renal tubular cell injury is caused by an event, and to delete the limitation related to development or proneness to develop acute renal failure. Express and/or inherent support is found, for example, in para. 0042.

Claim 37 is amended to delete the objected-to reference to "cardiovascular surgery"; to add as an event a cardiovascular event (express, verbatim support is found, for example, at para. [0063]); and to delete the phrase "the onset of".

Claim 38 is amended to provide that the mammalian subject is a patient in an intensive care unit (express support is found, for example, in para. [0042]).

Claim 39 is amended to delete "predict" and "determine the likelihood of" the acute renal tubular cell injury.

Claim 40 is amended to correct antecedent basis to acute renal tubular cell injury.

Claim 46 is amended to more particularly describe and distinctly claim the invention. The preamble is amended to provide for determining the presence of an acute renal tubular cell injury (inherent support is found, for example, in the original claim that provides "detection" of a renal tubular cell injury, and express support is found, for example, in para. [0063], the last sentence of para. [0100] and the last sentence of para. [0101] for "acute" renal injuries). The claim is also amended in step (c) to provide correlating the detected antibody-

NGAL complex from step (b) to the presence of the acute renal tubular cell injury (express support is found, for example, in paragraphs [0098], [0128] and [0129]).

New Claim 47 depends from claim 46 and provides that the step of detecting the antibody-NGAL complex further comprises determining the level of antibody-NGAL complex, and wherein the level of antibody-NGAL complex correlates with the extent of renal tubular cell injury (as supported, for example, at paras. [0043], [0098], [0100] and [0101]).

New claim 48 depends from claim 1 and provides that the detecting step further comprises determining the level of antibody-NGAL complex, and wherein the step of correlating comprises correlating the level of antibody-NGAL complex to the extent of the acute renal tubular cell injury. (Support again is found, for example, at paras. [0043] and [0101]).

New claim 49 depends from claim 1 and provides that the mammalian subject is prone to develop acute renal failure secondary to the acute renal tubular cell injury. Express and inherent support is found, for example, at paras. [0038] and [0045].

New claim 50 depends from claim 30 and provides that the acute renal tubular cell injury is an acute ischemic renal tubular cell injury (support is found, for example, in original claim 1, and paras. [0037], [0041], and [0054]).

New claim 51 depends from claim 30 and provides that the injury is an acute nephrotoxic injury (support is found, for example, in original claim 1, and paras. [0037], [0041], and [0054]).

New claim 52 depends from claim 30 and provides that the sample is an unprocessed urine sample. Support, can be found, for example, in para. [0078]. Furthermore, processing of urine samples is a routine procedure that is commonly used and well known to persons skilled in the art.

New claim 53 depends from claim 30 and provides that the mammalian subject is prone to develop acute renal failure secondary to the acute renal tubular cell injury. Express and inherent support is found, for example, at paras. [0038] and [0045]).

New claim 54 depends from claim 31 and provides that the method is used to predict acute renal failure secondary to acute renal tubular cell injury. Express and inherent support can be found, for example, in paras. [0038], [0045] and [0101].

New claim 55 depends from claim 31 and provides that the level of NGAL correlates with the extent of renal tubular cell injury. Express and inherent support can be found, for example, in paras. [0043] and [0101].

New claim 56 depends from claim 46 and provides that the mammalian subject is prone to develop acute renal failure secondary to the acute renal tubular cell injury. Express and inherent support is found, for example, at paras. [0038] and [0045].

New claim 57 is a new independent claim, similar to amended independent claim 1, wherein the step of correlating includes correlating the detected antibody-NGAL complex to the development of acute renal failure secondary to the acute renal tubular cell injury. Support can be found, for example, in paras. [0038], [0045] and [0101].

New step 58 depends from claim 57 and provides that the detecting steps comprises determining the level of antibody-NGAL complex, and wherein the step of correlating comprises correlating the level of antibody-NGAL complex to the extent of the acute renal tubular cell injury. Support again is found, for example, at paras. [0043] and [0101].

New claim 59 is a new independent claim, similar to amended independent claim 30, but where the acute renal tubular cell injury caused by an event, the event selected from the group consisting of: (a) a surgical procedure selected from the group consisting of cardiac surgery, coronary bypass surgery, and vascular surgery; (b) kidney transplantation; and (c) administration of a nephrotoxic agent. Support is found, for example, in paras. [0038] and [0063].

The claim amendments are either expressly, inherently, or impliedly supported by the disclosure as specified. No new matter has been added by way of the claim amendments.

Interview

Applicants wish to thank Examiners Ms. Christine Foster and Mr. Long Le for the courtesies and time provided at the interview conducted at the Office on November 7, 2007, attended by Applicants' attorney D.F. Nesbitt, inventor Dr. Prasad Devarajan, and Dr. Audrey Bartnicki, Esq., a representative of Abbott Laboratories. Applicants acknowledge the Interview Summary prepared by the Examiner and signed by Applicants' attorney following the interview, which is incorporated herein by reference.

Election/Restrictions (pages 2-7 of the Action)

The Examiner acknowledges Applicants' traversal in the reply filed 3/12/07, but finds it unpersuasive.

The Examiner considers the requirement proper and makes it FINAL.

The claims of Groups II-IV (claims 6-8, 12-23, 24-27 and 29) have been canceled without prejudice.

Acknowledgement of Examiner's Entry of Claim Amendments (page 8 of the Action)

Applicants wish to thank the Examiner for accepting the amendments submitted 3/12/07, in the interest of expediting prosecution, including ones that did not literally comply with 37 CFR 1.121 with respect to underlining and brackets.

Information Disclosure Statement (IDS) (pages 8-10 of the Action)

The Examiner states that the IDS filed 7/24/06 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP 609.

The Examiner considers that the reference by Matthaeus et al. entitled "Co-Regulation of Neutrophil..." fails to identify the complete journal name of the publisher or date of publication, and has not been considered by the Examiner. Applicants have obtained another copy of the Matthaeus et al. reference that includes the publisher and date information, and submitted the same for the Examiner's reconsideration in a Supplemental Information Disclosure Statement mailed November 13, 2007.

Applicants acknowledge that the Examiner has only considered the foreign document WO 2004/005540 to the extent of the English abstract submitted.

Applicants also acknowledge that the Examiner has not considered the Vinayak et al. reference, which the Applicant will address in a subsequent Supplemental Information Disclosure Statement.

Applicants further acknowledge that the Examiner has only considered pages 477-485 and 487 of the non-patent journal by Devarajan et al. entitled "Novel biomarkers for the early prediction", 2005; page 486 includes only part of the list of references cited in the subject journal. Applicants submitted a complete copy of this reference in the aforementioned Supplemental Information Disclosure Statement.

Supplemental Information Disclosure Statement

As mentioned above, Applicants have submitted a Supplemental Information Disclosure Statement on November 13, 2007 that includes additional references which the Applicants request the Examiner to consider.

In particular, the Supplemental Information Disclosure Statement includes two references cited in the corresponding examination of the equivalent European Patent Appln. 04758356.2.

The reference Pawluczyk et al., Biochimica et Biophysica Acta, 1645 (2003) 218-227 (Febr 21, 2003) was cited by a third party submission against the application, along with prior-identified references Mishra (2003) and Blaser (1995).

The reference Moses et al., Cancer Research 58, 1395-1399, 1998 (April 1, 1998) was cited by the European examiner in an action dated July 3, 2007, along with prior-identified references Matthaeus et al., Blaser and Ohlsson et al. (2003).

Priority (page 11 of the Action)

The Examiner has denied Applicants' claim for benefit of prior-filed US provisional patent application 60/458,143 (hereinafter, "the priority application"), for failing to provide adequate support or enablement in the manner provided by first paragraph of 35 USC 112, for one or more claims of the present application.

Applicants traverse.

a. The Denial of the Priority Claim is improper.

The Examiner supports the denial of priority claim based on the provision of 37 CFR 1.78(4) that the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the provisional), and that the disclosure of the invention in the provisional application must be sufficient to comply with the requirements of 112, 1st paragraph, citing *Transco Products, Inc. v. Performance Contracting, Inc.*. The Examiner finds that the disclosure of the prior-filed provisional application fails to provide adequate support or enablement in the manner provided by 35 USC 112, 1st paragraph for one or more claims of the benefit-claiming application.

Applicants believe that the rationale for denying the priority benefit does not properly state the priority claiming requirements under 35 USC 119(e)(1) and 37 CFR 1.78(4). Rule 1.78(4) provides that the provisional application disclose the invention claimed in at least one claim of the benefit-claiming non-provisional application, and to do so in the manner provided by the first paragraph of 35 U.S.C. 112. Applicants understand the phrase "the invention claimed in at least one claim" to mean "an invention read upon by at least one claim". The broader generic claim relating to "renal tubular cell injury" in the non-provisional application, includes the species inventions of ischemic and nephrotoxic injuries. It is undisputed that the ischemic injury species invention is disclosed in the provisional application in a manner sufficient to comply with the requirements of 112, 1st paragraph. Therefore, the provisional application satisfies Rule 1.78(4).

By contrast, the rejection of priority claim in the Action presumes that the full scope of the at least one claim of the non-provisional must find "adequate support and enablement" in the disclosure of the provisional application. This does not appear to be the law.

The recent case of *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 63 USPQ2d 1843, 1846 (Fed. Cir. 2002), deals with the inadequacy of disclosure in the provisional of the claimed invention of the non-provisional application. In *New Railhead*, the

distinguishing limitation of the broad claim (the angling of the unitary bit body with respect to the sonde housing) had not been disclosed in the provisional application, and had only been introduced upon filing of the non-provisional application. The applicant had publicly used the invention, including the distinguishing limitation, on a date prior to the filing date of the provisional application, and more than one year prior to the filing of the non-provisional application. The Federal Circuit opinion states that the district court correctly held that the disclosure of the provisional application does not adequately support any invention claimed in the '283 patent **as to the angle limitation**. (emphasis added). The entire claim scope required the angle limitation. The opinion also states that "the district court assumed, in considering the remaining summary judgment motion, that the '743 patent was entitled to the priority date of the provisional application" (emphasis added). Even though the provisional application made no mention at all of the distinguishing limitation of the broad claim (the angling of the unitary bit body with respect to the sonde housing), the district court nevertheless assumes that the non-provisional was entitled to the priority claim to the date of the provisional; it just was not entitled to that date for the distinguishing limitation in the claim.

Applicants therefore believe that the priority claims to both US Provisional Applications 60/458,143 and 60/481,596 meet all the requirements of 35 USC 119(e) and 37 CFR 1.78(4), and can not be denied. The Applicants request that the Examiner reconsider and *withdraw* the denial of priority claim to provisional 60/458,143.

b. Applicants' provisional application fully supports at least one pre-amended claim

Notwithstanding the above, Applicants point out that the provisional application 60/458,143 discloses "a reliable, early biomarker for renal injury would be useful to facilitate early therapeutic intervention, and help guide pharmaceutical development by providing an indicator of nephrotoxicity" (page 1), and that "the method of the invention can be used to detect the onset of ischemic renal injury, and to monitor the treatment thereof, for a wide variety of events that can include all varieties of diminished blood supply to the kidneys, impaired heart function, surgical procedures, patients in intensive care units, and the administration of pharmaceuticals, radiocontrast dyes, or other medicament substances to a subject" (page 12 and claim 22). The description above inherently discloses that NGAL as a nephrotoxic marker, useful to detect nephrotoxic injury in subjects, caused by administration

of pharmaceuticals, radiocontrast dyes, or other medicament substances. Consequently, a person of ordinary skill would conclude that the provisional application 60/458,143 provides adequate support for NGAL as both an ischemic and nephrotoxic marker of renal injury. Thus, even under the errant rationale in the Action, the disclosure of the prior-filed provisional application provides adequate support and enablement in the manner provided by 35 USC 112, 1st paragraph for one or more claims of the benefit-claiming application.

Specification (page 12 of the Action)

Applicants acknowledge and thank the Examiner for identifying certain errors in the disclosure and abstract. Correction of the errors in the disclosure and abstract have been made.

Claim Objections (pages 12 of the Action)

The Examiner objects to claims 2-5 and 9-11, because it is alleged, all dependent claims should be grouped together with the claim or claims to which they refer to the extent practicable, and although a dependent claim may refer to any preceding independent claim, in the instant case, the dependent claims refer to subsequent independent claims, which is improper.

Applicants request reconsideration.

MPEP 608.01(n) provides that in situations where a claim refers to a numerically following claim and the dependency is clear, as Applicants believe in the present case, both as presented and as it will be renumbered at issue, all claims should be examined on the merits and no objection as to form need be made. In such cases, the examiner will renumber the claims into proper order at the time the application is allowed.

Applicants also note that there are claim amendments which, if all claims are cancelled and renumbered, would not be discernible in accordance with the Office claim amendment rules. Therefore, Applicants suggest that the examiner accept the claim amendments submitted herewith, and that the Examiner then permit the Applicants to then submit a subsequent claim set that renumbers and orders the post-amended claims.

Claim Rejections

I. Claims 1-5, 9-11, 28, 30-40 and 46 are rejected under 35 USC 112, first paragraph (pages 13-20 of the Action)

A. Claim 1, 28, 30-40 and 46 are rejected for lacking support in the specification for amendments made to the claims. (pages 13-20 of the Action)

The Examiner rejects the claims as containing new matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1, 30 and 46 recited that the mammalian subject "is suspected of having or [is] prone to develop a renal tubular cell injury". Claim 34 referred to an event that "causes the mammalian subject to have, or be prone to developing, the renal tubular cell injury". The Examiner states that support could not be found in the specification for the limitation that the mammalian subject is "prone to developing a renal tubular cell injury", or for events that cause such subjects to be prone to developing the renal tubular cell injury.

Claims 36-38 recited an event that makes the subject develop or be prone to develop acute renal failure. The Examiner first states that the description of events in paragraph [0042] are not described as those that make the subject develop or be prone to developing acute renal failure, and thus the claimed genus differs from that disclosed in the description. The Examiner also says that claim 36-38 depend from claim 35 that recites samples obtained *at specific times in relation to the claimed event*, such that support could not be found for sampling at the specific times recited in relation to the claimed events, and specifically for 6, 4, 2, 1 hours and 30 minutes of "coronary bypass surgery", since this term could not be found in the description. Also the Examiner suggests that support could not be found for cardiovascular surgery, or for sampling within specific times of vascular surgery. Also the Examiner suggests that support could not be found for the sampling in relation to the *onset of* stroke, trauma, sepsis and dehydration, and to patients admitted to an intensive care unit.

Claims 34-35, and 28, recited sampling within 24 hours after an event, or alternatively within 6, 4, 2, 1 hours and 30 minutes. The Examiner concludes that the cited support is not commensurate in scope, since the claim scope including the time periods, in not limited to the specific scope of the examples. The Examiner states that the "onset of the event" may not

actually result in an immediate onset of injury. Para. [0051] mentions detecting a biomarker with the time periods referring to the renal tubular cell injury.

Claim 39 recites the method to "predict, diagnose, monitor or determine the likelihood of a renal tubular cell injury". The Examiner finds that the Applicants' cited support does not "clearly describe using the claimed method to predict, diagnose, monitor or determine the likelihood of renal tubular cell injury". In particular, the Examiner could not find support for "predicting" or for determining the likelihood of renal tubular cell injury.

Claim 40 recites the method wherein the NGAL level is "contrasted with a urinary NGAL level that distinguishes a subject that has a renal tubular cell injury from a subject that does not have the injury". The Examiner finds that the specification does not clearly disclose urinary NGAL levels that distinguish a subject that has a renal tubular cell injury from a subject that does not have the injury.

Applicants traverse in part and request reconsideration in part.

The Examiner's one-to-one correlation of every event with every sampling time (example, sampling times after vascular surgery) is an excessively restrictive requirement for support that the law, the rules and the practice do not contemplate. Verbatim (*in haec verba*) support in the disclosure of a claim term added by amendment is not required. See Ex parte Kevin P. Leahy et al., BPAI Decision 1999-0944. The decision by the Board summarizes the requirements for support of amended claims nicely:

> "the claimed subject matter need not be described *in haec verba* in the specification in order for the specification to satisfy the "written description" requirement of § 112, first paragraph, *In re Smith,* 481 F.2d 910, 914, 178 USPQ 620, 624 (CCPA 1973), and all new language added by amendment is not *ipso facto* new matter. *In re Wright,* 343 F.2d 761, 767, 145 USPQ 182, 188 (CCPA 1965)" … the examiner, in making a rejection under the "written description" requirement of § 112, first paragraph, must meet the requisite burden of proof by providing reasons why one of ordinary skill in the art would not consider the description sufficient. If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. *In re Alton,* 76 F.3d 1168, 1175, 37 USPQ2d 1578, at 1584. (emphasis added)

Applicants note out that the examiner has not presented any evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the remaining amended claims, but has only merely noted that the amended terms were not found, presumably, verbatim.

a) Traverse

Regarding **claim 35**, Applicants traverse. Applicants believe that the disclosure provides express support for the numerous time periods included in the claim, as amended. Applicants invite the Examiner's attention to Figures 4A, 4B, and 5, all of which show sampling of urine from rodents experiencing renal ischemia, taken at times 2, 4, 6, 8, 12 and 24 hours after clamping the renal artery(ies); Figure 6 that shows sampling of urine from rodents experiencing renal ischemia, taken at times 3, 6, 12 and 24 hours after clamping the renal artery(ies); Figures 12 and 13 that show urine NGAL detection in the urine of rodents at times 3 and 12 hours after injection of cisplatin; para. [0101] and Figure 16, showing urinary NGAL measurements in the urine of patients undergoing cardiopulmonary bypass (CPB) at times 2, 4, 6, 8, 12, etc. hours after bypass; and to para. [0051], which states

> "a method and a kit of the present invention can detect the RTCI biomarker in a sample of urine within four hours, more typically within two hours, and most typically within one hour, following renal tubular cell injury. Preferably, the RTCI biomarker can be detected within about 30 minutes following renal tubular cell injury."

A person of ordinary skill in the art would have understood that sampling times for human patients and for other events that result in acute renal tubular cell injury would have been firmly within the Applicants' possession at the time of the invention.

Regarding **claim 40**, Applicants traverse. Applicants believe that Example 5, para. [0100], provides clear, implicit support for claim 40. Paragraph [0100] states in part

> "…Urine from normal human controls … contained almost undetectable amounts of NGAL, indicating that upregulation of urinary NGAL is specific to acute renal injury *(not shown)*. Also, urine from patients with urinary tract infections and kidney transplant rejection (two neutrophil-related disorders) contained only minimal

quantities of NGAL (not shown), easily distinguishable from the significantly greater quantities in cadaveric kidney transplants (>100 ng/ml)…."

A person of ordinary skill in the art would have understood that acute renal tubular cell injuries result in levels of NGAL in the urine that are significantly greater in quantity compared to the lower level of NGAL in the urine of a mammal that does not have an acute renal tubular cell injury, such as normal mammals (including humans) and other disorders such as urinary tract infections and kidney transplant rejections, and that these different quantities of urinary NGAL can be compared and contrasted. The person of ordinary skill in the art would have understood that this invention would have been firmly within the Applicants' possession at the time of the invention.

b) Request for Reconsideration

To progress examination as to the remaining amended claims, and without acquiescing to the rejection, Applicants have abandoned some of the rejected claims without prejudice, and have made certain other amendments to the remaining rejected claims, and request reconsideration of the rejection of the remaining claims 1, 28, 30-34, 36-39 and 46 under 35 USC 112, first paragraph, for failing to provide adequate support for the claim amendments.

Claims 1, 30, 32, 34 and 46 have each been amended to provide that the mammalian subject is suspected of having an acute renal tubular cell injury. The support for "prone to develop acute renal failure" (e.g., as set forth in newly added claims 49, 53 and 56) is found at para. [0038] ["The use of the kit [for the rapid detection of urinary NGAL] can represent the standard of care for all patients who are at risk of developing ARF, including use in cardiac surgery, kidney transplantation, stroke, trauma, sepsis, dehydration, and nephrotoxins (antibiotics, anti-inflammatory agents, radio-contrast agents, and chemotherapeutic agents). In current clinical practice, when ARF occurs in the setting of these predisposing conditions,…]; and at para. [0045] ["…A typical sample can range from about 1 µl to about 1 ml…. Typically, these small amounts of urine are easily and readily available from clinical subjects who are either prone to developing ARF, or have developed ARF."]

Applicants have amended **claim 28** to provide that the sample is obtained within 24 hours of an acute renal tubular cell injury caused by an event. Applicants have amended

claim 35 to provide that the period of time follows the acute renal tubular cell injury caused by the event. These amendments are believed to align the scope of the claims explicitly with the disclosure and the examples, albeit some events and the onset of injury can occur at the same time, such as by clamping a renal artery.

Applicants also have amended **claim 37** to delete "cardiovascular surgery" and "the onset of", and to add "a cardiovascular event. The Applicants invite the Examiner's attention to para. [0063] regarding cardiovascular events. Applicants believe that a condition such as stroke, trauma, sepsis and dehydration would be well understood by a person of ordinary skill in the art, in view of the specification, as events that can cause, but not necessarily always cause, an acute renal tubular cell injury.

Claim 38 has been amended to provide that "the mammalian subject is a patient in intensive care that has experienced the event".

Finally, Applicants have amended **claim 39** to further limit the diagnosis and monitoring to acute renal tubular cell injury, and to delete the predicting and determining the likelihood of acute renal tubular cell injury.

B. Claims 2-5, 9-11, 28, and 30-40 were rejected for failing to enable all methods of "evaluating renal tubular cell injury status". (pages 20-23 of the Action)

The Examiner rejects these claims as lacking enablement for all methods of "evaluating renal tubular cell injury status". The Examiner states that the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with the claims. The Examiner considers that the term "evaluating renal tubular cell injury status" covers diagnostic methods of detecting renal tubular cell injury by measuring the level of NGAL in urine samples, but would also encompass methods of predicting, monitoring, determining the likelihood of injury, determining the extent of injury, and monitoring the effectiveness of a treatment for renal tubular cell injury.

The Examiner notes that the specification does not provide a specific or limiting definition for this term. Applicants now understand the Examiner's concern to be that the term "evaluating renal tubular cell injury status" encompasses other forms of "evaluating status" that are not described in the specification, such as determining the cause of an injury (which the specification does not describe or support), predicting the likelihood of a patient recovery, predicting the risk of recurrence, predicting the risk of mortality, etc.

The Examiner goes on to suggest, for example, that absent data to suggest that NGAL levels might be correlated with future risk of mortality, one skilled in the art would face an undue burden of examination given the laborious and lengthy nature of biomarker validation. [Applicants are confused by this statement. Perhaps the Examiner means that one skilled in the art would face an undue burden of experimentation?] The Examiner goes on to say that the state of the art teaches the unpredictability associated with clinical use of biomarkers even after a biomarker has been correlated with a specific disease state.

To progress examination forward, and without acquiescing to the rejection, Applicants have amended claims 28 and 30 to define the method as determining the presence of an acute renal tubular cell injury. At least one dependent claim further provides that the method is for determining the extent of the acute renal tubular cell injury. These claim amendments, which are expressly, inherently or impliedly supported by the disclosure, supra, render the rejection moot.

II. Claims 1, 28, 33, 40 and 46 are rejected under 35 USC 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention". (pages 23-24 of the Action)

The Examiner rejects claims 1, 28 and 46 as being incomplete for omitting essential steps, such omission amounting to a gap between the steps.

Applicants thank the Examiner for calling these to the Applicants' attention. Applicants have amended the claims to address the rejection, and request reconsideration and withdrawal of the rejection.

The Examiner states that Claim 33 recites the limitation "the onset of renal tubular cell injury", and concludes that there is insufficient antecedent basis for this limitation in the claims.

Applicants believe that the cited support, paragraph [0039], provides express support for this limitation. Nevertheless, in the interest of progressing examination of the application, Applicants have amended claim 33 to provide "detecting NGAL in the first urine output following the acute renal tubular cell injury".

The Examiner also states that claim 40, claiming a urinary NGAL level that distinguishes a subject that has a renal tubular cell injury from a subject that does not, has metes and bounds that are unclear because the specification does not define or clearly exemplify what value or values of NGAL levels would be considered to distinguish normal versus disease subjects. The Examiner concludes that one skilled in the art would not know based on the specification whether a particular NGAL level would fall within the scope of the claims or not.

Applicants request reconsideration and withdrawal of the rejection in view of the claim amendments. Applicants note that the Examples provide express support of the claimed invention as amended, and a working example of an NGAL level that distinguishes a subject as having an acute renal injury, from a subject that does not have an acute renal injury, namely:

> paragraph [0100] - "Urine from normal human controls or from patients with chronic renal failure contained almost undetectable amounts of NGAL, indicating that upregulation of urinary NGAL is specific to acute renal injury (not shown)";

as well as from a subject with an acute renal injury of such severity that it progresses to acute renal failure:

> Figure 16 and paragraph [0101] – "In the 10 patients who did not develop acute renal failure, there was small early increase in urinary NGAL excretion (2 hour values of 6.0±2.0 ng/mg creatinine) that rapidly normalized to almost undetectable levels within 12 hours post surgery (panel A). In marked contrast, patients who subsequently developed acute renal failure displayed a greater than 10-fold increase in the 2 hour value for urinary NGAL (75±10 ng/mg creatinine), and a greater than 20-fold increase in the 4 hour value for urinary NGAL (120±12 ng/mg creatinine)."

The examples provide an express description of the practice of the claimed invention, including a particular patient group, sampling time, and assay type. The level of skill in this art is high. Applicants believe that the person of ordinary skill, guided by the teaching of the specification and without undue experimentation, would have no difficulty in selecting a particular level or range of NGAL with which to distinguish a subject with an acute renal injury from a normal subject, and a subject having an acute renal injury that progresses to acute renal failure from a subject having an acute renal injury that does not.

III. Claims 1-2, 28, 30-37, 39-40 and 46 are rejected under 35 USC 102(a) as being anticipated by Mishra et al. (J. Am Soc Nephrol 14 (October 2003). (pages 24-27 of the Action)

The Examiner rejects the claims as anticipated by Mishra et al. The Examiner states that Mishra et al. teaches correlating the renal tubular cell injury status of the subject with elevated NGAL levels, which would read on the broadly claimed step of "evaluating the renal tubular cell injury status of the subject". The Examiner considers that Mishra et al., in its teaching of NGAL expression over the course of a disease, teaches monitoring of renal tubular cell injury. The Examiner states that Mishra et al. is available as prior art because Applicants were not entitled to a priority claim to Applicants' prior-filed provisional patent application 60/458,143.

a) Applicants are entitled to the claim of priority to provisional appln. 60/458,143

Applicants traverse, based on the arguments provided herein before that clearly show that Applicants are entitled to the claim of priority to US provisional patent appln. 60/458,143, and that the teaching of Mishra are fully covered in the provisional application.

b) Mishra et al. is Applicants' own work, and in not available as prior art.

Applicants note that the work conducted and disclosed in Mishra et al. and relied upon by the Examiner, was conceived and directed by the Applicants Barasch and Devarajan. Provided herewith is a Declaration under 37 CFR 1.132 by Drs. Devarajan and Barasch, which states that the work described in Mishra et al. and any statements therein that were relied upon by the Examiner as a basis for the rejection, is all and only their own work and statements, and not the work or statements of any of the other authors of Mishra et al., and not the work or statements of another person.

Because Mishra et al. is not available as prior art to the present application, Applicants respectfully request that the rejection under 35 USC 102(a) be withdrawn.

IV. Claims 1 and 46 are rejected under 35 USC 102(b) as being anticipated by Venge et al. (US 6,136,526) in light of the evidence of iHOP and Potempa (US 5,405,832) (pages 27-29 of the Action)

The Examiner states "Venge et al. teach methods of diagnosing human disease by measuring the level of HNL in [a] sample from a subject such as urine (see in particular the abstract and column 1, line 50 to column 2, line 26)"; and "Venge et al. further teach assaying for NGAL in human patients with clinically diagnosed acute bacterial or viral infections, including patients with pneumonia, acute upper urinary tract infections, pleuritis, and septicaemia (column 8, line 27 to column 9, line 20)." The Examiner concluded that "(s)uch subjects are 'suspected of having or being prone to develop a renal tubular cell injury' as claimed in light of the evidence of Potempa, which teaches that "septicemia" is also referred to as 'sepsis'" and that "the instant specification indicates that patients with sepsis are at risk of developing acute renal failure [0038]), such that septicemia subjects of Venge et al. read on the claim limitations since they are at risk of developing acute renal failure, which is a type of renal tubular cell injury". (page 27 and 28 of the Office Action)

Applicants request reconsideration of the rejection in view of the amendments made to the claims.

Claims 1 and 46 have been amended to provide the step of "correlating the detected antibody-NGAL complex to the presence of the acute renal tubular cell injury". The claims recite a step of detecting acute renal tubular cell injury in the mammal, which is not disclosed by Venge et al.

V. Claims 5, 30 and 32-33 are rejected under 35 USC 103(a) as being obvious over Matthaeus et al. ("Acute Ischemic…") in view of Gold et al. (US 6,242,246), Ramsden et al. (US 4,640,909), Blaser et al. ("A sandwich enzyme…") and Moses et al. (US 7,153,660) or in the alternative, over Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al. (pages 29-34 of the Action)

The Examiner rejects the claims as obvious over a combination of the above 5 or 6 references. The Examiner attributes the following teachings to the references [with Applicants' comments]:

1. Matthaeus is alleged to teach that levels of NGAL are upregulated in response to ischemic renal injury in a rat model, while control animals displayed only minor expression of NGAL, demonstrating that renal injury and repair is associated with an upregulation of NGAL, which read on the claimed step of "evaluating the renal tubular cell injury status" of claim 30, since the investigating and correlating renal injury status with level of expressed NGAL over time represents "evaluation" of renal injury status. It further is alleged that although Matthaeus does not teach detecting NGAL in urine as claimed, it is well known that disease processes may produce changes in certain analyte levels, and measuring such analyte levels can be used to detect the presence of disease.

The Examiner also states that the rat studies in Matthaeus would have been obviously extended to diagnosing the disease in humans, and that it would have been "further obvious" to employ urine as the sample source, instead of kidney tissue, because isolating kidney tissue is very invasive and an "unsuitable method" for diagnosing renal injury in humans.

2. Gold et al. is cited as a very general example of where detected proteins from individuals at risk of disease can be used for diagnosis. [There is no mention of NGAL or lipocalins, or of specific diseases particularly relevant to the present invention. Gold et al.'s general teaching of the concept of a patient being "at risk" to a disease is noted.]

3. Ramsden et al. is cited to teach the very general concept of urine sampling as a non-invasive sampling means. [Applicants note that there are many circumstances where a urine sample may be a totally inappropriate and unworkable body fluid for detecting a particular protein; for example, creatinine, etc.]

4. Blaser et al. is cited to disclose sampling and detection of NGAL in the blood and urine. [Applicants note that Blaser appears to disclose detection of NGAL in urine of healthy donors only, who showed minimal levels of NGAL (8.1 ± 5.6 μg/L using their particular

NGAL ELISA). Applicants further note that there is no mention of any specific diseases of particular relevance to the present invention.]

5. Moses et al. is cited by the Examiner to teach that NGAL may be detected in human urine by Western Blot. [Applicants note that Moses more specifically relates to patients with cancer in humans, and teaches detection of MMP in the urine, and more particularly with detection of complexes of MMP-9 with NGAL in urine, and the role of NGAL as an indicator of a TRAC (a tissue remodeling-associated condition, such as cancer).]

6. Ohlsson et al. is cited to teach an ELISA method to detect NGAL in blood plasma from a subject, all of who the Examiner presumes to be "at risk" of developing a renal injury. The Examiner states that Ohlsson et al. specifically looked at patients with ANCA-associated systemic vasculitis and recorded development of renal failure, and further teaches evaluating the renal tubular cell injury status based on the level of NGAL, in that Ohlsson et al. teach that *greatly elevated NGAL levels are strongly correlated with decreased renal function* (emphasis in the original). The Examiner states that giving Applicants' "evaluating the renal tubular cell injury status" its broadest interpretation", Ohlsson et al. meets the limitation. [Applicants note that Ohlsson et al. discloses sampling and detecting NGAL in the serum in patients as a measure of neutrophil degranulation. Ohlsson et al. used cystatin C as a marker for renal function. Ohlsson et al. does not disclose or suggest the sampling of urine from patients, or evaluating patients with acute renal injuries, including acute ischemic injury.]

Applicants request reconsideration and withdrawal of the rejection in view of the amendments to claims, and in view of the following arguments.

Matthaeus et al. teaches detecting gene expression in a post-ischemic kidney. Specifically, Matthaeus et al. discloses the study of the expression of the molecules MMP-9 and TIMP-1, and the rat homolog of NGAL, and discloses work only with excised kidney tissue. Matthaeus et al. does not discuss, demonstrate or suggest sampling of the urine. Matthaeus et al. addresses the processes involved in post-ischemic injury and repair, and selected samples for evaluating gene expression after 24 hours and 48 hours from the ischemic event. Matthaeus et al. mentions that NGAL might be associated and involved in some unspecified way with MMP-9 activation in renal injury.

The methodology used by Matthaeus et al. involves homogenizing the whole ischemic kidney to measure NGAL protein and mRNA. The assays tell the researchers that the kidney

contains NGAL protein and mRNA, but not the location of the protein or mRNA in the kidney. Matthaeus et al. appears to attribute the location of the NGAL mRNA and protein to the proximal tubules, the site of the injury.

Matthaeus et al. does not address immediate or early detection of acute renal injury at times less than 24 after the ischemic event, and does not demonstrate that NGAL is a biomarker for acute ischemic injury that can appear in the urine within 24 hours of the onset of the event. Matthaeus et al. also does not mention at all renal injuries caused by toxins. These facts underscore that the focus of Matthaeus is on post-injury repair.

Matthaeus et al. suggests that the NGAL mRNA and protein were expressed in injured proximal tubuli of the ischemic kidney, but does not suggest or disclose that expression of these compounds in this particular region of the kidney will result in the presence of NGAL protein in the urine. It is well known to persons of ordinary skill in the art that the proximal tubules are absorptive epithelia that remove, rather than express, a protein from the blood. The accompanying Declaration under 35 USC 1.132 by co-inventor Dr. Jonathan Barasch establishes that it is known that NGAL protein appearing in the proximal tubules does not pass into the urine. Mori et al., cited in the Declaration, explains that NGAL captured in the proximal tubuli is degraded to smaller fragments. Therefore, the NGAL protein alleged to appear in the proximal tubules would not later appear in the urine.

Matthaeus et al. mentions an ischemic event, but does not explain the type, extent and duration of the ischemic event. Applicants' disclosure well illustrates that the extent of an acute renal tubular cell injury is proportional to the duration of the ischemic event, as well as the degree of the ischemia. The extent of acute renal tubular cell injury correlates with the level of NGAL expressed by the distal tubules into the urine, within the range of mild to severe injury. Mattheus et al. does not describe if the ischemic event (clamping, for example) lasted for minutes, or hours, or was unilateral (only one kidney artery clamped) or bilateral (both).

Matthaeus et al. teaches that complexes of NGAL and MMP and/or TIMP-1 are upregulated in the proximal tubules in a rat model of ischemia. But such complexes would not be found, and are not found, in the urine of the ischemic rat. Matthaeus et al. does not disclose sampling of any body fluid within 24 hours of a renal injury. Applicants believe that a person of ordinary skill in the art, in view of Matthaeus et al., would not have considered

NGAL as a biomarker of renal injury, any more or less than they would considered TIMP-1 or MPP-9 as a biomarker of renal injury.

The Examiner also stated that it would have been "further obvious" to employ urine as the sample source, instead of kidney tissue, because isolating kidney tissue is very invasive and an "unsuitable method" for diagnosing renal injury in humans. However, the technique employed in Matthaeus is particularly well-suited for obtaining the sought-after information about gene expression at a particular site or body tissue. By contrast, the information sought by Matthaeus et al. – to determine the extent of co-expression of MMP-9, TIMP-1 and NGAL in the kidney proximal tubules – would not have been provided by sampling urine from the subject. Thus, a person of ordinary skill in the art would not find it obvious to employ Applicants' claimed sampling method in view of Matthaeus et al.

In conclusion, the combination of Matthaeus et al. and/or Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al. fails to state a prima facie obviousness rejection of Applicants' claims, and does not make obvious the invention of claims 5, 30 and 32-33, or of other claims depending therefrom. Applicants request that the rejection be withdrawn.

VI. Claims 1, 4, 9-11, 28, 31, 34-36, 39-40 and 46 are rejected under 35 USC 103(a) as being obvious over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., – and further in view of David et al. (US 4,376,110) (pages 34-37 of the Action)

The Examiner rejects the claims as obvious over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., previously addressed, in view of David et al. The Examiner cites David et al. as teaching a sandwich or "two-site" immunoassay for detecting the present of analytes in fluids, using an unlabeled capture antibody bound to a media, followed by a second labeled antibody that binds to a different site on the analyte.

The Examiner goes on to state that with respect to claims 28 and 34-36, Matthaeus et al. teach that NGAL was elevated "after 24 and 48 hours" of ischemia by Western blot, but that it would have been obvious to one of ordinary skill to detect NGAL "within 24 hours" out of the normal desire to improve upon what is already known. The Examiner mentions MPEP 2144.05, which pertains to the obviousness of claimed range that "overlap or lie inside ranges disclosed by the prior art" in order to establish a *prima facie* case of obviousness.

Applicants traverse.

First, Applicants believe that the claims are patentable in view of the failure of the combination of Matthaeus et al. and/or Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al. to state a prima facie obviousness rejection of Applicants' claims 5, 30 and 32-33.

David et al. represents general knowledge to persons of skill in the art about a wide variety of details about sandwich ELISA assays, and would be "relevant" to a wide variety of inventions related to detection of proteins and other compounds. However, this reference discloses nothing particularly relevant about Applicants' claimed invention.

As to claims 28 and 34-36, the claimed ranges are "within 24 hours", meaning "less than 24 hours". The cited reference Matthaeus et al. teaches "after 24 and 48 hours". Thus, there is no overlap of the claimed range with that of Matthaeus et al.

For the record, Applicants believe that some response is needed to other assertions made by the Examiner. The Examiner's rationale for why the authors of Matthaeus et al., or a person of ordinary skill in the art, would have wanted to gather samples within a time range "within 24 hours", and more particularly within the narrower time ranges claimed by Applicant, was "to diagnose disease earlier". Mattheaus et al. does not appear to be

concerned with "diagnosing disease". The cause of the injury was clear – renal ischemia, presumably caused by clamping of either or both arteries to the kidneys. Matthaeus et al. appears to be concerned with repair of the injury and other "post-injury" issues.

The Examiner also states a "reasonable expectation of success" because the assay of David et al. is "more sensitive", so that "upregulation of NGAL would be reasonably expected to be detectable at earlier time points than by Western blot (as performed by Matthaeus et al.)". The Examiner presumes that Matthaeus et al. sampled after 24 hours because of a lack of sensitivity of the analytical tool to detect the protein or gene expression product. That seems speculative at best, since Applicants can see no particular barrier to excising the kidney sample at any time prior to 24 hours. The time-dependent event is the excising and processing of the kidney sample. Once excised, the sample can be evaluated by the Western blot at the researcher's discretion. Therefore, contrary to the Examiner's presumption, the sampling time selected by Matthaeus et al. is independent of the sensitivity of the analytical tool to detect the protein or gene expression.

VII. Claim 2 is rejected under 35 USC 103(a) as being obvious over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., or in the alternative, Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al. -- and further in view of Valkirs et al. (US 2003/0109420) (page 37 of the Action)

The Examiner rejects the claim as obvious over Matthaeus et al. and/or Ohlsson et al., in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., previously addressed, in view of Valkirs et al. The Examiner cites Valkirs et al. as teaching the value of testing multiple samples from the same individual, to identify changes in levels of markers over time, and that such data provide information about disease status, including appropriateness of drug therapies and identification of patient outcome. [Applicants note the Examiner's recognition of the general teaching of the concept of a patient's disease status being determined based on the level of markers in multiple samples and over time.]

Applicants traverse.

The claim is patentable in view of the amendments and arguments previously presented with respect to the claim(s) from which claim 2 depends. Valkirs et al. represents general knowledge to persons of skill in the art about markers for acute coronary syndrome, and may be "relevant" to a wide variety of inventions related to the markers for a wide variety of diseases. This reference's discloses does not appear to be particularly relevant to Applicants' claimed invention.

VIII. Claim 2-3 are rejected under 35 USC 103(a) as being obvious over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., or in the alternative, Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., -- and further in view of Linzer et al. (US 3,635,091) (page 38 of the Action)

The Examiner rejects the claims as obvious over Matthaeus et al. and/or Ohlsson et al., in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., previously addressed, in view of Linzer et al. The Examiner cites Linzer et al. as teaching a urine sample collector wherein the subject urinates continually into the container to collect the urine in two or more fractions.

Applicants traverse.

The claims are patentably distinct in view of the amendments and arguments previously presented. Furthermore, this reference's disclosure does not appear to be particularly relevant to Applicants' claimed invention.

IX. Claim 33-38 are rejected under 35 USC 103(a) as being obvious over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., or in the alternative, Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., – and further in view of Muramutsu. (Kidney International) (page 38-40 of the Action)

The Examiner rejects the claims as obvious over Matthaeus et al. and/or Ohlsson et al., in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., previously addressed, in view of Muramatsu. The Examiner cites Muramatsu as teaching that it is imperative to diagnose acute renal failure (ARF) as soon as possible, and that disease markers that can be measured in blood or urine would "be of extreme value" since ARF is associated with high morbidity and mortality.

The claims are patentably distinct in view of the amendments and arguments previously presented. Furthermore, this reference's discloses does not appear to be particularly relevant to Applicants' claimed invention, except to point out a secondary consideration in Applicants' favor for the importance of finding NGAL as an immediate, non-invasive, selective, and sensitive biomarker of acute renal tubular cell injury.

Double Patenting (Pages 41-43)

Claims 1-5, 9-11, 28, 30-40 and 46 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over the claims 1-20 of co-pending Application No. 11/374,285 (Applicants' commonly-owned attorney docket CHM-032).

Claims 1-5, 9-11, 28, 30-40 and 46 are also provisionally rejected on the ground of non-statutory obviousness-type double patenting over the claims 1-20 of co-pending Application No. 11/096,113 (Applicants' commonly-owned attorney docket CHM-025M), in view of Ramsden et al., Blaser et al. and Moses et al.

Applicants acknowledge the Examiner's non-statutory obviousness-type double patenting rejections, but traverse and request reconsideration.

Applicants traverse with the Examiner's conclusion that the claims of the current application are not patentably distinct from the claims of co-pending Application No. 11/374,285 (Applicants' commonly-owned attorney docket CHM-032). The present claims provide a method to detect an acute renal tubular cell injury by measuring NGAL protein in urine in a subject having or prone to developing ARF. The claims of the co-pending Application No. 11/374,285 provide a method to detect chronic renal tubular cell injury by measures NGAL protein in urine, blood, serum and other body fluids, in a subject having a chronic renal disease (CRD). Applicants consider that the claims of the present application are patentably distinct from the claims of co-pending Application No. 11/374,285.

Applicants also traverse with the Examiner's conclusion that the claims of the current application are not patentably distinct from the claims of co-pending Application No. 11/096,113 (Applicants' commonly-owned attorney docket CHM-025M). The present claims provide a method to detect an acute renal tubular cell injury by measures NGAL protein in urine in a subject having or prone to developing ARF. The claims of the co-pending Application No. 11/096,113 provide a method to detect an acute renal tubular cell injury by measuring NGAL protein in blood or serum in a subject having or prone to developing ARF. Applicants refer the Examiner to the record in co-pending Application No. 11/096,113, as well as the arguments and record here, that make it clear that NGAL in the blood and the NGAL in urine are from distinct sources, and represent separate and distinct pools of NGAL. The arguments of record make it clear that the existence of a blood NGAL assay would not provide a reasonable expectation of success in developing a urine NGAL

assay. Therefore, Applicants consider that the claims of the present application are patentably distinct from the claims of co-pending Application No. 11/096,113.

CONCLUSION

Applicants believe a full and complete response to the Action has been made.

Respectfully submitted,

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